UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,061	08/31/2001	Jean-Yves Bonnefoy	PF86PCTSEQ	1138

7590 09/08/2004

G Patrick Sage
The Firm of Hueschen & Sage
500 Columbia Plaza
350 East Michigan Avenue
Kalamazoo, MI 49007-3856

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,061	BONNEFOY ET AL	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27,28,30,31 and 35-48* is/are pending in the application.

4a) Of the above claim(s) *40-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,27,28,30,31 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☒ Other: *Sequence search report (one)*.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments and Response

1) Acknowledgment is made of Applicants' amendments filed 06/28/04 and 12/08/03 and Applicants' response filed 03/29/04. Applicants' response filed 06/28/04 has been considered. The elected claims, as amended, have been examined. Applicants should note that this Office Action is made Final as necessitated by Applicants' amendments to the claims.

Status of Claims

2) Claims 26, 29, 30 and 32-34 have been canceled via the amendment filed 12/08/03.

Claims 25, 27, 28, 31 and 35-39 have been amended via the amendments filed 12/08/03 and 06/28/04.

Claims 25, 27, 28, 30, 31 and 35-48 are pending.

Claims 25, 27, 28, 30, 31 and 35-39 are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicant's Information Disclosure Statement filed 12/08/03. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Objection(s) Withdrawn

4) The objection to the drawings made in paragraph 7 of the Office Action mailed 08/29/03 is withdrawn in light of Applicants' submission of formal drawings on 12/08/03.

5) The objection to claim 31 made in paragraph 16 of the Office Action mailed 08/29/03 is withdrawn in light of Applicants' cancellation of the claim.

Objection(s) Maintained

6) The objection to the specification made in paragraph 8 of the Office Action mailed 08/29/03 is maintained for reasons set forth therein.

Rejection(s) Moot

7) The rejection of claims 26, 29, 30 and 32-34 made in paragraph 9 of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as containing adequate written description, is moot in light of Applicants' cancellation of the claims.

8) The rejection of claims 26, 29, 30 and 32-34 made in paragraph 10 of the Office Action

mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claims.

9) The rejection of claims 26, 29, 30, 32 and 34 made in paragraph 12(a) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

10) The rejection of claim 29 made in paragraph 12(b) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claim.

11) The rejection of claim 26, 29 and 30 made in paragraph 12(d) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claims.

12) The rejection of claim 26 made in paragraph 12(f) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claim.

13) The rejection of claim 32 made in paragraphs 12(g), 12(h) and 12(l) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claim.

14) The rejection of claim 26, 29, 30 and 32-34 made in paragraph 12(j) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

15) The rejection of claim 26, 29, 30 and 32-34 made in paragraph 14 of the Office Action mailed 08/29/03 under 35 U.S.C. § 102(a) as being anticipated by Andreoni *et al.* (WO 99/49892A2), is moot in light of Applicants' cancellation of the claims.

16) The rejection of claim 26, 29, 30 and 32-34 made in paragraph 15 of the Office Action mailed 08/29/03 under 35 U.S.C. § 102(b) as being anticipated by Binz *et al.* (WO 9741888-A1), is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

17) The rejection of claims 25, 27, 28, 31 and 35-39 made in paragraph 9 of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as containing adequate written description,

is withdrawn in light of Applicants' amendments to the claims and/or the base claim.

18) The rejection of claims 25, 27, 28, 31 and 35-39 made in paragraph 10 of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicants' amendments to the claims and/or the base claim.

19) The rejection of claims 25, 36 and 38 made in paragraph 12(a) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims and/or the base claim.

20) The rejection of claim 25 made in paragraph 12(c) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

21) The rejection of claims 25 and 31 made in paragraph 12(d) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims and/or the base claim.

22) The rejection of claim 25 made in paragraph 12(e) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

23) The rejection of claim 27, 28, 31 and 35-39 made in paragraph 12(j) of the Office Action mailed 08/29/03 under 35 U.S.C. § 112, first paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims and/or the base claim.

24) The rejection of claim 27, 28, 31 and 35-39 made in paragraph 14 of the Office Action mailed 08/29/03 under 35 U.S.C. § 102(a) as being anticipated by Andreoni *et al.* (WO 99/49892A2), is withdrawn in light of Applicants' amendments to the claims and/or the base claim. A modified rejection is made below.

25) The rejection of claim 27, 28, 31, 35, 38 and 39 made in paragraph 15 of the Office Action mailed 08/29/03 under 35 U.S.C. § 102(b) as being anticipated by Binz *et al.* (WO 9741888-A1), is withdrawn in light of Applicants' amendments to the claims and/or the base claim. A modified rejection is made below.

Response to Applicants' Arguments

26) With regard to the disclosure of Binz *et al.* (WO 9741888-A1), Applicants acknowledge that

Binz *et al.* disclose oligosaccharide antigens coupled to the P40 OmpA protein and the use of this P40 OmpA protein as a protein carrier of oligosaccharides for improving the immune response against an oligosaccharide antigen in a mammal. Applicants contend that Binz *et al.* does not disclose nor suggest that P40 OmpA is capable of binding to an APC and be internalized into the APC with the coupled active substance. Applicants submit that they have demonstrated in Example 6 and Figure 4 of the specification that other carrier proteins, such as TT or BB, are not capable of binding to APCs and thus are not internalized by APCs. Applicants conclude that the capability of a carrier to enhance an immune response to an associated antigen is not inherent in its capacity to bind APCs or to be internalized within these cells.

With regard to the disclosure of Andreoni *et al.*, Applicants contend that Andreoni *et al.* do not disclose nor suggest that P40 OmpA is capable of specifically binding to APCs and to be internalized by these APCs together with the active substance coupled with P40. Applicants allege that the Office has not identified a *prima facie* basis for an anticipation rejection. Applicants argue that the cited references do not disclose or suggest a method to specifically deliver an active substance into APCs by coupling the active substance with the P40 OmpA protein as claimed.

Applicants' arguments have been carefully considered, but are non-persuasive. It should be noted that the method claimed in the instant claims, as amended, does not require or include the step of 'internalization into the APC'. Furthermore, the instant claims do not require that the P40 OmpA specifically binds to APCs. With regard to the APCs, the only requirement is that the biologically active substance coupled to the OmpA having the structure of SEQ ID NO: 2 is 'contacted' with antigen-presenting cells, irrespective of whether the 'contacting' takes place *in vitro* or *in vivo*. The two references used in the art rejection taught the two required steps of the claimed method: a) covalently coupling a biologically active substance to the OmpA protein having the amino acid sequence of SEQ ID NO: 2 chemically, or recombinantly by genetic fusion; and b) contacting the coupled biologically active substance with antigen-presenting cells. Clearly, the Office has established a *prima facie* basis for anticipation.

New Rejection(s)

Applicants are asked to note the following new or modified rejection(s) made in this Office. The new rejections are necessitated by Applicants' amendments to the claims.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

27) Claims 25, 27, 28, 31 and 35-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 25 is confusing and/or lacks proper antecedence. In lines 3 and 6 of claim 25, for proper antecedence and definiteness, it is suggested that Applicants replace the recitation 'said active substance' and 'said coupled active substance' respectively with --said biologically active substance-- and --said coupled biologically active substance-- respectively.

(b) Analogous criticism applies to claims 38 and 39.

(c) Claims 27, 28, 31 and 35-39, which depend from claim 25, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

28) Claims 25, 27, 28, 31 and 35-39 are rejected under 35 U.S.C. § 102(a) as being anticipated by Andreoni *et al.* (WO 99/49892A2 , already of record; English translation provided).

Andreoni *et al.* taught a process of delivering a *Klebsiella* membrane protein as a pharmaceutical composition to improve a mammal's immunity to an antigen or hapten, i.e., a biologically active substance that is associated with it (see abstract and claims). The biologically active substance is a peptide, a polysaccharide, an oligosaccharide, or a nucleic acid, which is coupled covalently to the OmpA protein via an amino acid linker, i.e., attachment element, such as Cys, aspartic acid or ornithine (see Example 3; and claims 7 and 14-16). The OmpA protein is produced by extraction from an enterobacterial culture or by a recombinant process (see Examples 1 and 2; and claims 4 and 5). The amino acid sequence of the rP40 OmpA is depicted in pages 1 and 2 under 'Liste De Sequences', which meets the description of the amino acid sequence recited in the instant claims. The biologically active substance is a recombinant hybrid (i.e., chimeric) protein (see claim 17). That the prior art method involves the contacting of the biologically active substance coupled to rP40 with the mammal's antigen-presenting cells including dendritic cells is inherent from the teachings of Andreoni *et al.* in light of the fact that rP40 OmpA coupled to the biologically active substance inherently and necessarily comes in contact with antigen-presenting cells *in vivo* in the mammal's body to whom the coupled rP40 has been delivered.

Claims 25-39 are anticipated by Andreoni *et al.*

29) Claims 25, 27, 28, 31, 35, 36 and 39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Binz *et al.* (WO 97/41888-A1, already of record - English translation provided) as evidenced by Pease *et al.* (US 2004/0014207 A1).

The page numbers indicated below refer to the page numbers in the translated document.

Binz *et al.* disclosed a method of injecting (i.e., delivering) into the popliteal lymph nodes of rabbits the recombinant P40 OmpA protein of *Klebsiella pneumoniae* chemically and covalently coupled to a biolologically active substance, such as, a bacterial oligosaccharide (i.e., antigen or hapten). The recombinant P40 OmpA protein of *Klebsiella pneumoniae* has the amino acid sequence of SEQ ID NO: 2 having a 9 amino acid leader peptide sequence of the tryptophan operon, Met Lys Ala Ile Phe Val Leu Asn Ala (see pages 36 and 37; pages 15 and 39; and Example 8). The covalent coupling is accomplished via attachment elements, such as, ADH linkers (see page 13). The P40-oligosaccharide conjugate elicited high levels of IgG antibodies to the oligosaccharide (see Example 8). The prior art method, comprising the two instantly recited steps, inherently serves as a method of delivering the biologically active oligosaccharide coupled to the recombinant P40 OmpA protein of *Klebsiella pneumoniae* to antigen-presenting cells, including dendritic cells, because it is known in the art that dendritic APCs are present in the popliteal lymph nodes. For instance, see section [0127] of Pease *et al.* In this rejection, it should be noted that the prior art 9 amino acid leader peptide sequence of the tryptophan operon, Met Lys Ala Ile Phe Val Leu Asn Ala, corresponds to amino acid residues 1-9 of the instantly recited amino acid sequence of SEQ ID NO: 2 and the prior art amino acid sequence of SEQ ID NO: 2 corresponds to amino acid residues 10 through 344 of the instantly recited SEQ ID NO: 2. See the attached sequence search report.

Claims 25, 27, 28, 31, 35, 36 and 39 are anticipated by Binz *et al.* The reference of Pease *et al.* is **not** used as a secondary reference in combination with Binz *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Binz *et al.* ('273). See *In re Samour* 197 USPQ 1 (CCPA 1978).

Relevant Art

30) The art made of record and not relied upon currently in any of the rejections is considered pertinent to Applicants' disclosure:

- Goetsch *et al.* (US 2004/0014661 A1) establishes MKAIFVLNA amino acid sequence to be the tryptophan operon leader sequence. See section [0090] of Goetsch *et al.*

Remarks

31) Claims 25, 27, 28, 31 and 35-39 stand rejected.

32) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

33) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (703) 872-9306.

34) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

35) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week,

which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

September, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER

XX

DE Protein P40, and OMPA protein from K. pneumoniae I-145.

XX

KW Outer membrane protein; OmpA; P40; immunocomplex; oligosaccharide;
KW polysaccharide; vaccine; Salmonella.

XX

OS Klebsiella pneumoniae.

XX

PN WO9741888-A1.

XX

PD 13-NOV-1997.

XX

PF 06-MAY-1997; 97WO-FR00800.

XX

PR 07-MAY-1996; 96FR-0005692.

XX

PA (FABR) FABRE MEDICAMENT SA PIERRE.

XX

PI Sinz H, Haeuw JF, Svenson S;

XX

DR WPI; 1997-558694/51.
DR N-PSDB; AAV13867.

XX

PT Immunogenic complex for use in anti-bacterial vaccine - comprises
PT bacterial oligo- or polysaccharide coupled to a Gram-negative
PT bacterial outer membrane protein or a Streptococcal HSA binding
PT protein

XX

PS Claims 11,12,20; Page 35-36; 63pp; French.

XX

CC The patent discloses a new immunogenic complex which consists of (1) an
CC oligo- or polysaccharide found naturally on bacteria, coupled to (2) a
CC carrier protein chosen from (a) the human serum albumin binding protein
CC of Streptococcus, (b) Gram-negative bacterial outer membrane proteins
CC (Omp), or (c) fragments of these proteins. The immunogenic complex is
CC useful in a vaccines to protect animals against infection by Salmonella,
CC especially those belonging to antigenic specificity group O:9,
CC including S. enteritidis, S. panama and S. dublin. A vaccine prepared
CC using an oligosaccharide from S. enteritidis can be used to provide
CC protection against septicaemia caused by S. typhi and against typhoid

CC fever, as well as to protect humans and animals from toxic infections
CC and zoonosis caused by Salmonella of the same serogroup. The carrier
CC proteins enhance the immunogenicity of the oligo- or polysaccharide
CC antigens. Inclusion of additional Salmonella capsule antigens, such as
CC the Vi antigen, increases the vaccine's efficacy against encapsulated
CC bacteria. The present sequence, protein P40 from Kleb. pneumoniae
CC I-145, is a preferred example of a carrier protein which can be used
CC in the immunocomplex.

XX

SQ Sequence 335 AA;

Query Match 97.4%; Score 335; DB 18; Length 335;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 335; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          10 APKDNTWYAGGKLGWSQYHDTGFYGNGFQNNNGPTRNDQLGAGAFGGYQVNPYLGFEMGY 69
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db           1 APKDNTWYAGGKLGWSQYHDTGFYGNGFQNNNGPTRNDQLGAGAFGGYQVNPYLGFEMGY 60

Qy          70 DWLGRMAYKGSVDNGAFKAQGVQLTAKLGYPITDDLDIYTRLGGMVWRADSKGNYASTGV 129
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          61 DWLGRMAYKGSVDNGAFKAQGVQLTAKLGYPITDDLDIYTRLGGMVWRADSKGNYASTGV 120

Qy         130 SRSEHDTGVSPVFAGGVEWAVTRDIATRLEYQWVNNIGDAGTVGTRPDNGMLSLGVSYRF 189
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         121 SRSEHDTGVSPVFAGGVEWAVTRDIATRLEYQWVNNIGDAGTVGTRPDNGMLSLGVSYRF 180

Qy         190 GQEDAAPVVAPAPAPAPEVATKHFTLKSDVLFNFNKATLKPEGQQALDQLYTQLSNMDPK 249
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         181 GQEDAAPVVAPAPAPAPEVATKHFTLKSDVLFNFNKATLKPEGQQALDQLYTQLSNMDPK 240

Qy         250 DGSAVVLGYTDRIGSEAYNQQLSEKRAQSVVDYLVAKGIPAGKISARGMGESNPVTGNTC 309
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         241 DGSAVVLGYTDRIGSEAYNQQLSEKRAQSVVDYLVAKGIPAGKISARGMGESNPVTGNTC 300

Qy         310 DNVKARAALIDCLAPDRRVEIEVKGYKEVVTQPAG 344
               ||||||||||||||||||||||||||||||||||
Db         301 DNVKARAALIDCLAPDRRVEIEVKGYKEVVTQPAG 335
```